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# **BIRTH WEIGHT AND SUBCLINICAL CARDIOVASCULAR AND RENAL DAMAGE IN A POPULATION-BASED STUDY (THE STANISLAS COHORT STUDY)**

## **Running title: BIRTH WEIGHT AND ORGAN DAMAGE IN THE STANISLAS COHORT**

Marilucy LOPEZ-SUBLET<sup>(a,b)</sup>, Thomas MERKLING<sup>(b,c)</sup>, Nicolas GIRERD<sup>(b,c)</sup>, Constance XHAARD<sup>(b,c)</sup>, Adrien FLAHAULT<sup>(b,d)</sup>, Erwan BOZEC<sup>(b,c)</sup>, Celine LEROY<sup>(b,c)</sup>, Tomona FUJIKAWA<sup>(b,c)</sup>, Allan Arthur VAAG<sup>(e)</sup>, Alexandre MEBAZAA<sup>(b,f)</sup>, Caroline Michaela KISTORP<sup>(g)</sup>, Barbara HEUDE<sup>(h)</sup>, Jean Marc BOIVIN<sup>(b,c)</sup>, Faiez ZANNAD<sup>(b,c)</sup>, Sandra WAGNER<sup>(b,c)\*</sup>, Patrick ROSSIGNOL<sup>(b,c,i)\*</sup>.

*(a) AP-HP, Hôpital Avicenne, Centre d'Excellence Européen en Hypertension Artérielle, Service de Médecine Interne, Bobigny, France. INSERM UMR 942 MASCOT, Paris 13-Université Paris Nord.*

*(b) FCRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France.*

*(c) Université de Lorraine, INSERM CIC-P 1433, CHRU de Nancy, INSERM U1116, Nancy, France.*

*(d) Service de Néphrologie, Hôpital Européen Georges Pompidou, 20 rue Leblanc 75015 Paris.*

*(e) Steno Diabetes Center Copenhagen, Borgmester Ib Juuls Vej 83, 2730 Herlev, Denmark.*

*(f) UMR-S 942 INSERM, Lariboisière Hospital, Paris; Paris Diderot University, Sorbonne Paris Cité; Department of Anaesthesiology and Critical Care, Lariboisière Hospital, AP-HP, Paris.*

*(g) Department of Endocrinology, Copenhagen University Hospital, Rigshospitalet; Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.*

*(h) Université de Paris, Research Center in Epidemiology and Biostatistics (CRESS), INSERM, INRAE, Paris, France.*

*(i) Medicine and Nephrology-Hemodialysis departments, Princess Grace Hospital, and Monaco Private Hemodialysis Centre, Monaco, Monaco*

*\* Equal contribution*

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**Corresponding author:** Pr Patrick Rossignol

Centre d'Investigations Cliniques-INSERM CHRU de Nancy

Institut lorrain du Cœur et des Vaisseaux Louis Mathieu

4 rue du Morvan

54500 Vandoeuvre Lès Nancy

France

[p.rossignol@chru-nancy.fr](mailto:p.rossignol@chru-nancy.fr)

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## **Abstract**

### **Objective**

Although preterm-born and low-birth weight individuals have an increased risk of cardiovascular diseases in adulthood, little is known regarding early cardiovascular and renal damage (CVRD) or hypertension in adulthood. Our study investigated the association of birth weight with early CVRD markers as well as the heritability of birth weight in an initially healthy family-based cohort.

### **Methods**

This study was based on 1028 individuals from the familial longitudinal STANISLAS cohort (399 parents/629 children) initiated in 1993-1995, with a 4th examination conducted in 2011-2016. Analyses performed at the 4th visit included pulse wave velocity, central pressure, ambulatory blood pressure, hypertension status, diastolic dysfunction/distensibility, left ventricular mass (LVMI), carotid intima-media thickness and kidney damage. The family structure of the cohort allowed birth weight heritability estimation.

### **Results**

Mean ( $\pm$ SD) birth weight was  $3.3\pm 0.6$  kg. Heritability was moderate (42-44%). At the 4<sup>th</sup> visit, individuals were 37 years old [32.0-57.0], 56% were women and 13% had antihypertensive treatment. Birth weight was strongly and negatively associated with hypertension (OR 95%CI: 0.61 [0.45-0.84]). A non-linear association was found with LVMI, participants with a birth weight  $> 3$ kg having a higher LVMI. A positive association ( $\beta$  95%CI: 5.09 [1.8-8.38]) was also observed between birth weight and distensibility for adults with normal body mass index (BMI). No associations were found with other CVRD.

### **Conclusion**

In this middle-aged population, birth weight was strongly and negatively associated with hypertension, and positively associated with distensibility in adults with normal BMI and with LVMI for higher birth weights. No associations were found with other CVRD markers.

Keywords: Birth weight, cardiovascular and renal damage, arterial stiffness, intima-media thickness, echocardiographic diastolic dysfunction, microalbuminuria, renal disease, heritability.

## **Introduction**

Cardiovascular (CV) and chronic kidney diseases constitute major public health burdens as leading causes of disability and death.[1] The “Barker hypothesis”[2] proposes fetal origins of adult disease and is supported by many epidemiological studies. Low birth weight (LBW) (any live birth under 2500 grams, newborn under 2500 grams) and preterm birth (<37 weeks gestation) have emerged as predisposing factors of mortality as well as of cardiovascular, renal and metabolic morbidities in adulthood.[3,4] High birth weight (HBW) (newborn over 4000 grams) may also represent a risk or vulnerability factor predisposing to adult-onset diseases including cancer[5], although the risk of CV and renal disease for HBW subjects remains unproven.[6-8]

According to the World Health Organization (WHO), the worldwide prevalence of LBW varies from 15.5 to 16.5% and stands at 7.5% in France according to the national perinatal survey.[9] The WHO describes LBW as an emerging risk factor for chronic diseases such as cardiovascular disease[10], although the pathophysiological mechanisms of structural or functional damage between these births appear to differ and are not well understood. Moreover, the U-shaped[11] association between birth weight and adult mortality described by Baker et al.[4] in a Danish cohort of 216 464 subjects (over 43 years of follow-up) suggests that increased birth weight does not necessarily lead to improved health in adulthood.

The literature is consistent regarding CV risk and disease in preterm-born adults with higher blood pressure (BP) levels[12], increased risk of ischemic heart disease[13], early death from CV causes[14] and risk of ischemic stroke.[15] However, detailed analysis of this literature often does not allow for analysis of the LBW population since it is often excluded or remains unreported. The parameters that influence LBW are multiple, such as gestational age, undernutrition, impaired fetal blood supply, smoking in pregnancy or other toxic exposures which can separate the issues of prematurity and fetal growth restriction.[16]

On the other hand, few studies have been able to investigate the relationship between early impairment of endothelial function or vascular biomarkers[17], vascular stiffness and carotid, aortic and cardiac remodeling[16,18-21] in adults born preterm. Preterm birth or LBW has been found to lead to increased risk of coronary artery disease[4,22,23], atrial fibrillation[6], stroke[24], chronic renal failure[25] and hypertension in adulthood.[26]

The impact of HBW in adulthood on CVRD has been poorly studied, with the difficulty of distinguishing the influence of term at birth and gestational diabetes (whose relationship is well established).[27]

Finally, the genetic aspects of growth are seemingly complex and under multifaceted influences. A large number of studies have shown that the heritability of height is particularly high, allowing the latter to be determined for each individual. However, the nature of the heritability of birth weight is also seemingly complex. A recent genome-wide meta-analysis showed considerable genetic overlap between birth weight in twins and singletons.[28]

Taking advantage of the familial STANISLAS (Suivi Temporaire Annuel Non-Invasif de la Santé des Lorrains Assurés Sociaux) cohort comprising 2 generations and for which extensive CV and renal phenotyping has been performed[29], the objective of the present study was to investigate the relationship between birth weight on early target organ damage (CVRD) 15-20 years later. The heritability of birth weight was also studied.

## **Material and methods**

### **Study population**

The STANISLAS cohort is a population-based study of 1006 families each comprised of 2 parents and at least 2 children (4295 participants) from the Lorraine region (eastern France) recruited during 1993–1995 (visit 1, V1) at the Center for Preventive Medicine. The participants were of French origin and free of acute or chronic disease. From 2011-2016, 1705 participants underwent their 4th examination (V4). The STANISLAS study has been described in detail elsewhere.[29] After excluding 2506 participants without birth weight information (self-reported), and 1064 who did not attend the final

visit, the present analysis included 1028 participants in whom at least one outcome of interest was recorded (Figure 1).

The research protocol was approved by the local ethics committee (Comité de Protection des Personnes Est III, Nancy, France) and all study participants gave written informed consent to participate.

### **Data collection**

A self-reported questionnaire was used to collect socio-demographic information, including age, sex, generation 1 (parental generation n=399, 59.0 [56.0, 62.0] years) and generation 2 (who were children at the start of the study n=629, 33.0 [30.0, 36.0] years, median of 37 years [32.0, 57.0]) in both generations combined and adults at V4), smoking status, education level, income and birth weight, as well as information relative to disease history and treatment such as anti-hypertensive, lipid or glucose lowering drugs.[29] For children at visit 1, parents were asked to report birth weight, prematurity and breastfeeding of their children. Blood samples were collected at V1 and V4, spot urine samples were also collected at V4. The serum concentrations of the following biomarkers were measured: fasting glucose, HDL-C, LDL-C and triglycerides as well as urine concentrations of creatinine and microalbumin at V4 only. Anthropometric measurements such as weight, height, and waist circumference (WC) were conducted during a clinical examination. Twenty-four hour ambulatory blood pressure monitoring (ABPM) was performed as follows: participants underwent 24-hour recording of the ABPM using the Spacelabs 90207 ambulatory monitor (Spacelabs Medical), with the monitoring cuff placed around the non-dominant arm. The blood pressure system was programmed to take measurements every 15 minutes from 6 AM to 10 PM and every 30 minutes from 10 PM to 6 AM.

### **Cardiovascular assessments at V4**

#### ***Left ventricular mass indexed (LVMI) and diastolic dysfunction***

Echocardiographic examinations were performed in the left lateral decubitus position by an experienced echocardiographer using a commercially available standard ultrasound scanner (Vivid E9,

General Electric Medical Systems, Horten, Norway) with a 2.5-MHz phased-array transducer (M5S). The echocardiographic/Doppler examinations included exhaustive examinations in parasternal long- and short-axis views and in the standard apical views.[30] All acquired images and media were analyzed on a dedicated workstation (EchoPAC PC, version 110.1.0, GE Healthcare). Septal wall thickness, posterior wall thickness and left ventricular (LV) internal diastolic diameter were measured from the parasternal 2-dimensional long-axis view. These measurements were subsequently used in the cube-function formula of the American Society of Echocardiography Guidelines to calculate LV mass[31] which was then indexed for height to the 2.7 power.

Left ventricular diastolic dysfunction was assessed according to the EAE/ASE recommendations: mild or grade 1 (impaired relaxation pattern), moderate or grade 2 (pseudo-normal left ventricular filling), and severe (restrictive filling) or grade 3.[32] All grades were grouped together.

#### ***Carotid-femoral pulse wave velocity (cfPWV)***

cfPWV was measured using the Complior device (Alam Medical, France) in a quiet room after at least 10 minutes of rest in supine position according to the recommendations of the European Network for the Noninvasive Investigation of Large Arteries.[29,33]

Two sensors were placed simultaneously on the carotid artery and femoral artery. Two measurements were made, with cfPWV calculated as their mean. If the 2 measurements differed by  $> 0.5$  m/s, a third measurement was made, and the cfPWV was then calculated as the median of the 3 measurements. The onboard foot-to-foot algorithm based on the second-derivative waveforms was used to determine the transit time. The carotid-to-femoral, carotid-to-sternal-notch, and sternal-notch-to-carotid distances were measured with a measuring tape. The distance used for cfPWV calculation was 0.8 times the direct carotid-femoral distance, with cfPWV calculated as distance divided by transit time.

#### ***Carotid intima-media thickness (cIMT)***

cIMT measurements were routinely performed by high resolution echotracking (Wall Track System; Pie Médical) as previously described.[29] The noninvasive investigations were performed in a controlled environment at  $22 \pm 1^\circ\text{C}$  after 10 minutes of rest in supine position. IMT was measured on the right common carotid artery at 1 to 2 cm below the carotid bifurcation. The Wall Track System measures the parameters in 2 dimensions on 1 radiofrequency line perpendicular to the artery (7.5



MHz probe). The cIMT was assessed at the far wall. The retained value was the mean of 4 measurements. Carotid diameter, carotid distention (measured by the device) and distensibility (calculated by a formula involving the distension, the diameter and the local pulsed pressure measured with the SphygmoCor system), and cIMT were measured for the right common carotid artery. Four measurements were carried out per patient. Examinations were performed with a wall tracking system (ESOATE, Maastricht, The Netherlands) and/or the ART.LAB (ESAOTE) in immediate succession.

## **Blood pressure outcomes and hypertension**

### ***Hypertension***

Hypertension was defined as declared by the participants in their interview on medical history, or the intake of antihypertensive drugs or based on 24h-ABPM (>130 mmHg systolic blood pressure (SBP) or > 80 mmHg diastolic blood pressure (DBP)) with or without antecedent hypertension, but without underlying history of coronary artery disease (CAD) or heart failure (HF).

### ***Renal outcomes***

Estimated glomerular filtration rate (eGFR) was estimated using the CKD-EPI equation. eGFR change between the first and the 4th visit was calculated. Albuminuria was defined as the urine albumin-to-creatinine ratio (uACR) and dichotomized according the 90th percentile of the cohort (>90th percentile vs. lower values).

All blood-derived biosamples were stored in a central biobank facility at regulated temperatures between -80°C and -196°C as required (e.g. -196°C for plasma and serum). Circulating levels of multiple proteins, including neutrophil gelatinase-associated lipocalin (NGAL) were assessed at the 4<sup>th</sup> visit, using the Olink method with PEA as described in Ferreira et al.[29] NGAL levels are expressed in arbitrary units since they were measured with the Olink® technology standardized log<sub>2</sub> NPX values.

## **Statistical analyses**

Participant characteristics are first described according to birth weight classes ( $\leq 2.5$ ; 2.5-3; 3-3.5; 3.5-4; >4 kg). Percentages within each class are presented for categorical variables and mean (SD) or

median [Q1, Q3] for continuous variables, according to visual examination of distributions. Between-group assessments of participant characteristics were performed using ANOVA or Kruskal-Wallis test, depending on normality, for continuous variables and Fisher's exact or chi-square tests, for categorical variables.

We next investigated the association between birth weight and eGFR, albuminuria/creatininuria ratio, NGAL, LVMI, diastolic dysfunction (e' impairment), PWV, cIMT and distensibility. For each outcome, a separate complete-case population analysis was run to maximize sample size per outcome. Given the family structure of our cohort, the non-independence of family members was accounted for by using mixed models with a family random effect. For continuous outcomes, linear mixed models with the *lmerTest* [34] package were used. P-values for effects were calculated using the Kenward-Roger degrees-of-freedom correction and confidence intervals of estimates were estimated using the profile likelihood method. LVMI, cIMT and PWV did not meet the normality assumption and were thus log transformed. For binary outcomes, binomial generalized linear mixed models with a logit link function in the *glmmTMB* package were used.[35] P-values for effects were calculated using likelihood ratio-tests and confidence intervals of odds-ratio were estimated using the Wald method.

Nested models were run for each outcome, except for treated hypertension, albuminuria and diastolic dysfunction (see below). Model 1 was crude without adjustments; Model 2 was adjusted for age (standardized within generation and sex), sex, generation, education level, smoking status and physical activity, HDL, LDL, triglycerides, glycemia, lipid-lowering treatment (TTx), anti-diabetic TTx, anti-hypertensive TTx (except for hypertension as outcome) and SBP (except for hypertension as outcome); Models 3 and 4 consisted of Model 2 further adjusted for BMI or WC classes, respectively. All adjustment variables were (assessed at the 4<sup>th</sup> visit. Variation inflation factors (VIF) were all < 3 thereby indicating the absence of collinearity among adjustment variables.

The interaction between age and generation was also tested for each outcome. Given that this interaction was found significant for treated hypertension and eGFR decline, it was included in the adjusted models for these outcomes. Interactions between birth weight and generation, BMI or waist

circumference class were also tested. All continuous adjustment variables were standardized to facilitate model convergence.

Given the limited number of treated hypertension (N = 96), albuminuria (N = 82) and diastolic dysfunction (N = 101) events, Model 2 was adjusted for age, sex and smoking status only, while also further adjusting for BMI or WC class. No interactions were tested with these outcomes.

Sensitivity analyses were also performed whereby participants treated for HF or MI or with history of stroke or lower limb arteritis as well as participants born prematurely were removed.

The methodology for heritability estimation is detailed elsewhere. In brief, a dedicated linear mixed model implemented in the *gaston* R package was used.[36] Two models were run, one with the self-reported pedigree kinship matrix (Kinship) and the other with genetic relatedness matrix (GRM), the latter of which was computed using polymorphic SNPs from the GWAS data carried out at the 4<sup>th</sup> visit with the GSA Illumina® Chip. For the first model, all subjects with reported birth weight (BW) were included (n=2092) while for the second model, only subjects with successful genetic data were included (n=956). Only sex was used as covariate. Data pertaining to maternal status before and during pregnancy were not available. All analyses were conducted in R version 4.0.4.[37]

## **Results**

### **Characteristics of the population**

The median age of the overall population was 37 [32-57] years, 56% were women, 34% were hypertensive and 13% had dyslipidemia (Table 1). Their median BMI was 24.5 [22.0, 27.8] kg/m<sup>2</sup>, total cholesterol was 2.1 ± 0.4 g/L, and median ABPM 24-hour SBP and 24-hour DBP values were 118 [112, 125] and 73 [69, 78] mmHg, respectively. Mean (± SD) birth weight was 3.3 ± 0.6 kg.

Participants were older in the extreme classes of birth weight and hence more likely to be from generation 1, take anti-hypertensive treatments and have a low education level. There were fewer women in the HBW categories and there were a lower percentage of females who smoked. Waist

circumference and serum creatinine were higher for the highest birth weight, and preterm birth was more likely for the smallest birth weight.

### **Associations between birth weight and subclinical CV outcomes**

Birth weight was strongly and negatively associated with hypertension status defined by declared or treated hypertension or high BP ( $\geq 130/80$  mmHg in 24h ABPM) and treated hypertension alone (Table 2; Figure 2).

A non-linear association was found between birth weight and LVMI (Table 3), with only a positive association with birth weight  $\geq 3$ kg (slope for birth weight  $< 3$ kg:  $-0.03$  [ $-0.1; 0.04$ ];  $p = 0.48$ ; slope for birth weight  $\geq 3$ kg:  $0.05$  [ $0.01; 0.09$ ];  $p = 0.016$ ). However, this association was no longer present after adjustment for BMI or became marginal for WC class, both assessed at V4 (Table 3).

The association between birth weight and cIMT was dependent on BMI class, with a negative association only among overweight participants (Table 3). There was also a positive association between distensibility and birth weight, but only in the crude and adjusted models. The interaction with BMI class was also significant (Table 3), with a positive association found only among participants with normal BMI, not amongst overweight or obese participants.

Finally, there were no associations between birth weight and PWV or diastolic dysfunction.

Removing participants with CV diseases or prematurity did not alter the results (Table S1).

### **Associations between birth weight and renal outcomes**

Overall, there was no evidence of associations between birth weight and renal outcomes, i.e., NGAL, ACR, eGFR or eGFR decline (Tables 2 and 3).

### **Heritability of birth weight**

The heritability of birth weight was estimated at 42% to 44% according to the model used, with covariate effects (sex only) accounting for less than 4%, while more than 50% of the variance remained unexplained (Table S2).

## **Discussion**

The uniqueness of our study lies in the simultaneous and extensive measurements of early subclinical arterial, cardiac and renal damage according to birth weight in an initially healthy population-based cohort study (2 family generations). Our main finding was that birth weight was strongly and negatively associated with hypertension status in adulthood.

The link between BP level and birth weight has been documented in the literature, and described in a first systematic review published by Lawlor et al. in 1996.[24] The majority of the studies (n=34) reviewed showed that BP was inversely related to birth weight in children and adults. Huxley et al. conducted another systematic review which showed that birth weight and head circumference at birth were inversely related to SBP, although this relationship was attenuated in adolescence. Accelerated postnatal growth was also associated with raised BP.[3] In a large UK cohort of 25 874 employees comprised of men and women aged 17 to 64 years (mean age  $38.0 \pm 7.9$ ), Davies et al. showed that LBW predicted higher adult SBP (mean (SD), with the latter being higher in men compared to women (127(14) vs. 119 (14) mmHg).[38]

In a latest review published in 2020, Lewandowski et al. established that preterm birth was associated with an increased risk of CV diseases including ischemic heart disease and hypertension. The studies and recent meta-analyses in this latter review clearly established the link between preterm birth and higher BP whereby preterm-born adolescents and young adults featured a SBP of +3.4 to 4.2 mmHg and DBP of +2.1 to 2.3 mmHg compared with term-born peers. Being born prematurely resulted in an increased relative rate of antihypertensive drug prescription in adulthood. This review further highlighted that being born preterm was associated with a reduced cardiac reserve and smaller left and right ventricular volumes, as well as decreased vascularity, increased vascular stiffness, and higher pressure of both pulmonary and systemic vasculatures.[21]

In the present cohort, a non-linear association was found with LVMI, showing a positive association with a birth weight  $\geq 3$ kg. This latter association was no longer present however after adjustment for BMI or WC. Being born preterm is known to be associated with morphological and functional cardiac impairments across all developmental stages including neonatal life, infancy and adulthood.[18] Regarding cardiac remodeling according to birth weight, Vijayakumar et al. in 1995 examined ultrasound data from 290 men in England, and concluded that low weight at 1 year was associated with a concentric enlargement of LVMI in adult life and could be the long-term result of hemodynamic changes *in utero* or a persisting change in growth factor concentrations.[39] The following year, Zureik et al. studied SBP and ventricular mass in 210 subjects aged between 8 and 24 years. SBP was highest in subjects with LBW and LVMI was negatively related to weight at 9 months or 2 years.[40]

More recently, in a cohort of adolescents (n=1964) in the Avon cohort, HBW adjusted for sex and gestational age was associated with cardiac diastolic function in late adolescence along with a positive linear association between birth weight Z-score and LVMI.[41]

A negative association between LBW adults in overweight (BMI>25) and cIMT was furthermore observed in our population. In a review published by Norman et al. on LBW and vascular tree development, a total of 11 studies were tested for an association between birth weight and IMT. The results obtained were heterogeneous and did not allow concluding that early IMT occurs in the aorta and carotid arteries in conjunction with poor fetal growth.[42] More generally, the technical conditions (sometimes difficult) underlying the measurement of cIMT in patients with a high BMI should likely also be taken into account.

There was also a positive association in the present study between distensibility and birth weight, as well as an interaction with BMI class. This positive association was only found among participants with normal BMI, and not in overweight or obese participants. One hypothesis that has been repeatedly tested is that fetal growth restriction may accompany altered elastin synthesis in the aortic and other large artery walls which, in turn, could lead to a permanent loss of arterial elasticity.[42]

There were no associations herein between birth weight for PWV and diastolic dysfunction. A study conducted in 558 healthy teenagers in whom PWV was measured, no linear correlation was found

between birth weight and hemodynamic parameters.[43] Most studies have indeed failed to demonstrate a direct link between LBW and increased aortic or carotid stiffness, often due to lack of power.[42]

A systematic review conducted by Edward et al. revealed that SBP was higher in subjects born preterm than term, although no differences were observed in endothelial dysfunction or arterial stiffness.[44] The above reported observations would suggest that hypertension comes first, which in turn promotes vascular damage (increased atherosclerosis and vascular stiffness). Further studies are needed to confirm this hypothesis.

A multivariate analysis conducted in 2020 by Flahault et al. in a population of 86 preterm subjects followed over a period of 23 years showed that carotid and brachial arterial distensibility was lower in adults born preterm and that bronchopulmonary dysplasia (a frequent complication of extremely preterm birth) was associated with lower arterial distensibility.[16]

Kowalski et al. found high indices of wave reflection in the aortic arch and correlation with central systolic pressure in a cohort of 76 prematurely born adolescents.[20] Central aortic SBP was negatively related to birth weight, while in multivariable analysis, only preterm was associated with higher estimated central aortic SBP, leading the authors to suggest that the intensity of the waves could constitute a new sensitive marker of the evolution of vascular dysfunction.[20] Other authors comparing populations born at term versus those born prematurely (n=102 in each group) showed that while adults born preterm had significant differences in their aortic structure comparatively to adults born at term, they had relatively small differences in central arterial stiffness that may partially be explained by BP variations.[19]

More generally, there is a clustering of CV risk factors in the setting of inflammation and oxidative stress. When analyzing 101 healthy young adults born preterm, Flahault et al. showed that in this population, the usual associations between dysfunctions, including adiposity, elevated BP and glucose intolerance, were not observed in the preterm group as opposed to the full-term population, and markers of inflammation and oxidative stress were not higher in the preterm compared to the full-term group, despite higher rates of medical conditions.[45] In a review by Norman et al.

encompassing 20 studies involving 1500 subjects, approximately half affirmed the existence of endothelial dysfunction. However, the disparate results most likely stemmed from different population and age groups. Therefore, the causes of dysfunctional vascular tree associated with poor fetal growth remain to be clarified.[42]

On the other hand, for renal damage, the first systematic review of observational studies between birth weight and renal function appeared in 2009. In their study, White et al. demonstrated a link between birth weight and kidney disease, with LBW increasing the risk of developing kidney disease later in life by 70%.[25]

Prematurity is also likely linked to increased risk of kidney dysfunction and high BP in childhood and into early adulthood. Premature birth was found to confer a twofold increased risk of CKD.[46,47] Our current study also analyzed renal function since several literature reviews have highlighted prematurity and/or LBW as a marker of impaired nephrogenesis and is related to chronic kidney disease (CKD). Laucyte-Cibulskiene et al. studied the influence of several factors in sum (birth weight, prematurity, discrepant birth weight ratio and postnatal growth mismatch phenotype combined) on initial kidney damage. The authors acknowledged that while low birth weight can influence renal damage, there are also other factors to take into account such as exposure during development to unfavorable environments acting on the kidney. This can lead to a decrease in nephron number/podocyte endowment, hence the necessity to identify early life factors that affect kidney function over the life course, including reporting of sex-stratified analyses.[48] In summary, the authors stated that history of prematurity (regardless of sex) and lower birth weight in women were factors associated with a lower eGFR based on cystatin C, whereas in men, a history of low birth weight (z-score) was a risk marker for albuminuria in adulthood. More importantly, the eGFR equations derived from cystatin C showed a greater ability to detect these outcomes compared to creatinine-based eGFR equations.[48] In our study, however, we did not observe any association between birth weight and renal outcomes in our cohort sample, whether NGAL, ACR, eGFR or eGFR decline. These results could be explained in part by the limited choice for the calculation of renal function, in which only creatinine values were available and eGFR could only be estimated



with a creatinine-based equation, and by the fact that our population consisted of healthy subjects with a median eGFR of 100 ml/min/1.73m<sup>2</sup> (vs. 73 ml/min/1.73m<sup>2</sup> in the Laucyte-Cibulskiene et al. study) with only 6 participants (less than 1%) with an eGFR < 60 ml/min/1.73m<sup>2</sup>. The reasoning underlying the possible relationship (cause or consequence) with hypertension in our population thus does not appear to be directly related to nephropathy, but likely to other cardiovascular damage, hemodynamic mechanisms (e.g. early kidney dysfunction compensated by hyperfiltration due to high BP) or CV risk per se including hypertension.[44]

A study of normal kidney function in a young adult population born with LBW (n=552) published by Vasarhelti et al. suggested that signs of early glomerular and tubular impairment were not present. In addition, high BP in LBW individuals may be the result of abnormally high sodium excretion. There appears to be an alteration of NA<sup>+</sup>/K<sup>+</sup>-ATPase activity that may be indirectly linked with either the elevation of BP and/or in the enhanced natriuresis in this population.[49]

Finally, in the present study, we analyzed the heritability of birth weight, which was estimated between 42% and 44% according to the model used, with covariate effects (sex only) accounting for less than 4%, while more than 50% of the variance remained unexplained.

The fetal origins of adult diseases have resulted in a paradigm shift in the way we view determinants of disease. Previously, genetic inheritance and adult lifestyle factors were considered as the primary contributors to disease. However, currently, the discussion of genetic confounding of the fetal origins of CV diseases has created some controversy especially on the role of *in utero* environmental factors.[50]

Magnus et al. estimated the risks of LBW as a function of parental birth weight in a study of 67,759 families examining paternal, maternal and offspring correlations in birth weight. The authors concluded that paternal birth weight was a significant and independent predictor of LBW in offspring. Heritability of birth weight in their study was estimated at 25%.[51]

In a large Swedish twin study on the fetal origins of hypertension, Bergvall et al. found that decreased birth weight was associated with an increased risk of hypertension independently of genetic factors, shared familial environment, as well as risk factors for hypertension in adulthood, including BMI.[50]

On the other hand, in another twin study, Ijzerman et al. were unable to exclude the possibility that the association between birth weight and adult blood pressure was at least partly mediated or confounded by genetic factors.[52]

### **Study limitations**

Information on birth weight in the present study was only declarative. Our cohort data did not have the premature status and breastfeeding data for all individuals, or the gestational age to assess whether LBW was appropriate for gestational age or the result of intrauterine growth restriction. Data regarding maternal status before and during pregnancy were not available, in particular the presence of hypertensive disorders of pregnancy or gestational diabetes for HBW. This remains a limitation of the current analysis since it notably includes hypertension disorders of pregnancy and CV risk factors, among others.

Another limitation of our study is that GWAS data were not sufficient to allow calculating the birth weight Polygenic Risk Score, and thereby to assess how genetic factors that influence birth weight may have impacted adults, in particular hypertension. Brøns et al. have recently reported an association between severe metabolic disturbances and increased liver fat in LBW children, which was independent of birth weight as well as T2D polygenic risk scores indicating non-genetic factors to explain the associations.[53]

### **Perspectives**

Birth weight is a variable that is often accessible but remains misunderstood in epidemiology. Birth weight is strongly associated with mortality risk during the first year and, to a lesser degree, with developmental problems in childhood as well as the risk of various diseases in adulthood.

In the present middle-aged population, birth weight was strongly and negatively associated with hypertension and positively associated with distensibility in adults with normal BMI and with LVMI for higher birth weight individuals. The heritability of birth weight was moderate.

While our main result is in agreement with the literature regarding the strong and negative association between birth weight and hypertensive status, the design of the study may provide additional value over previous studies. Indeed, the lack of association between birth weight and other early CV and renal outcomes in a 2-generation cohort at low risk with simultaneous measurements of classical early CV and renal early markers, opens the prospect of finding other factors that may influence these relationships, such as growth and vascular age, BMI, pregnancy data, nutrition, etc.

Additional studies aimed at analyzing all of the factors related to the birth of a newborn, including maternal conditions before and during pregnancy as well as the birth conditions of the newborn, will allow a better understanding of organ development and of inherent pathophysiological mechanisms for the prevention of CVRD using early predictive markers, including taking into account the influence of heritability.

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**Figure legends**

Figure 1: Flowchart of the study population in the STANISLAS cohort

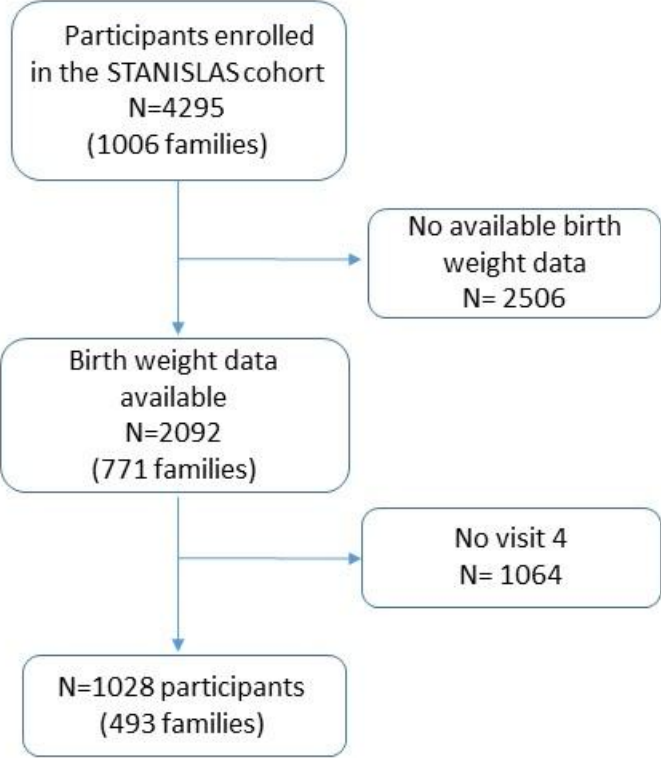
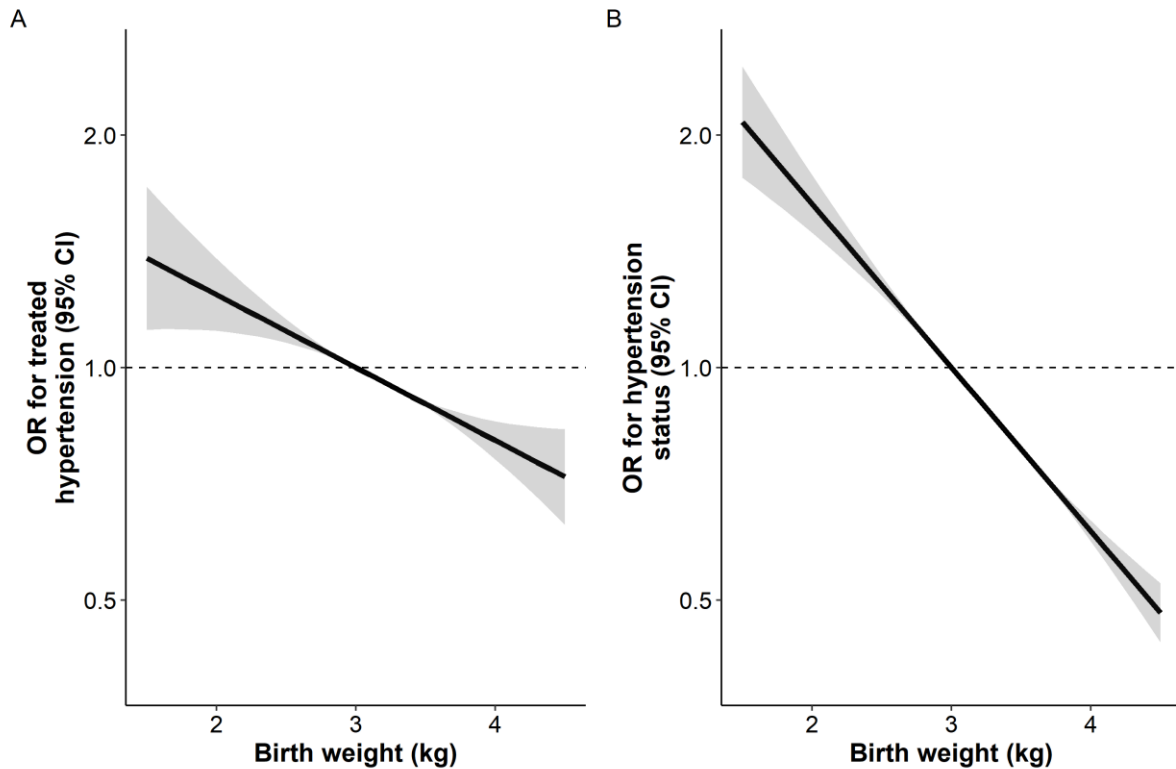


Figure 2: Association between birth weight and A) treated hypertension or B) hypertension status (declared or treated hypertension or high blood pressure  $\geq 130/80$  mmHg 24h ambulatory blood pressure monitoring).



### Table legends

Table 1: Characteristics of participants at visit 4 according to birth weight class

Table 2: Association of birth weight with dichotomous cardiovascular and renal outcomes at visit 4

Table 3: Association of birth weight with continuous cardiovascular and renal outcomes at visit 4

### Supplementary files legends

Table S1: Sensitivity analyses for the association between birth weight and each outcome without prematurity and CV diseases

Table S2: Percentage of variance decomposition for birth weight

List S1



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**Table 1: Participant characteristics at visit 4 according to birth weight class**

	Overall	N	≤ 2.5 kg	2.5 - 3 kg	3 - 3.5 kg	3.5 - 4 kg	> 4 kg	p
N	1028		81	205	429	236	77	
Age (yrs)	37.0 [32.0, 57.0]	1028	55.0 [35.0, 60.0]	38.0 [33.0, 58.0]	37.0 [31.0, 56.0]	35.0 [30.8, 56.0]	55.0 [32.0, 59.0]	<0.001
Women (%)	573 (55.7)	1028	64.2	66.8	57.6	46.2	36.4	<0.001
Generation 2 (%)	629 (61.2)	1028	42.0	54.6	67.1	69.9	39.0	<0.001
Smoking status (%)		1024						0.017
Current smoker	263 (25.7)		13.6	21.0	28.4	28.9	26.0	
Never smoker	476 (46.5)		54.3	53.2	46.0	42.1	36.4	
Past smoker	285 (27.8)		32.1	25.9	25.6	28.9	37.7	
Education level (%)		1025						0.051
< High school degree	294 (28.7)		42.0	30.2	26.3	24.6	36.4	
0-2 years after high school	392 (38.2)		34.6	35.6	38.5	40.3	41.6	
> 2 years after high school	339 (33.1)		23.5	34.1	35.2	35.2	22.1	
Income (%)		1023						0.633
<1500€/month	131 (12.8)		13.6	16.1	12.7	11.1	9.2	
1500-2249€/month	189 (18.5)		19.8	14.6	18.1	20.9	22.4	
2250-2999€/month	198 (19.4)		21.0	17.1	19.0	22.6	15.8	
3000-4999€/month	362 (35.4)		32.1	41.5	33.8	32.3	40.8	

	<b>Overall</b>	<b>N</b>	<b>≤ 2.5 kg</b>	<b>2.5 - 3 kg</b>	<b>3 - 3.5 kg</b>	<b>3.5 - 4 kg</b>	<b>&gt; 4 kg</b>	<b>p</b>
>5000€/month	112 (10.9)		11.1	8.8	13.1	9.4	9.2	
Does not know or refuses to answer	31 (3.0)		2.5	2.0	3.3	3.8	2.6	
BMI (kg/m <sup>2</sup> )	24.5 [22.0, 27.8]	1027	24.1 [22.1, 28.9]	23.8 [21.4, 27.0]	24.5 [21.9, 27.8]	24.9 [22.7, 28.2]	25.0 [22.7, 29.6]	0.036
BMI class (%)		1027						0.114
Normal weight	557 (54.2)		56.8	59.5	54.2	50.4	49.4	
Obese	162 (15.8)		21.0	13.2	13.3	18.2	23.4	
Overweight	308 (30.0)		22.2	27.3	32.5	31.4	27.3	
Waist circumference (cm)	87.0 [77.0, 97.0]	1019	87.0 [78.0, 99.0]	82.0 [74.0, 94.0]	86.0 [76.0, 96.0]	90.0 [81.0, 98.0]	90.0 [82.0, 100.0]	<0.001
High WC (%)	260 (25.5)	1019	32.1	24.4	23.7	27.4	26.3	0.517
Physical activity (MET/min)	1647 [594, 4158]	868	1519 [594, 4309]	1440 [480, 4224]	1698 [594, 3576]	1507 [613, 3994]	2648 [960, 6132]	0.070
Energy intake (kcal/d)	2244 [1753, 2897]	1022	2261 [1757, 2801]	2199 [1695, 2826]	2212 [1729, 2876]	2280 [1825, 2903]	2523 [1779, 3132]	0.162
Premature (%)		1028						<0.001
No	207 (20.1)		1.2	12.7	21.7	30.1	20.8	
Yes	40 (3.9)		13.6	5.4	3.3	0.8	2.6	
Missing	781 (76.0)		85.2	82.0	75.1	69.1	76.6	
Breastfeeding (%)		1028						0.007

	<b>Overall</b>	<b>N</b>	<b>≤ 2.5 kg</b>	<b>2.5 - 3 kg</b>	<b>3 - 3.5 kg</b>	<b>3.5 - 4 kg</b>	<b>&gt; 4 kg</b>	<b>p</b>
No breastfeeding	68 (6.6)		3.7	7.3	5.6	8.5	7.8	
< 4 weeks	60 (5.8)		4.9	3.4	7.7	4.2	7.8	
> 4 weeks	118 (11.5)		6.2	7.3	11.4	18.2	7.8	
missing	782 (76.1)		85.2	82.0	75.3	69.1	76.6	
Anti-hypertensive TTx (%)	140 (13.6)	1028	21.0	17.6	12.8	8.1	16.9	0.009
Fasting glycemia (g/L)	0.9 [0.8, 0.9]	987	0.9 [0.8, 0.9]	0.9 [0.8, 0.9]	0.9 [0.8, 0.9]	0.9 [0.8, 0.9]	0.9 [0.8, 0.9]	0.086
Glucose lowering TTx (%)	25 (2.4)	1028	3.7	2.4	2.6	1.7	2.6	0.820
Diabetes (%)	32 (3.1)	1024	3.7	3.4	3.3	2.1	3.9	0.834
Triglycerides (g/L)	0.9 [0.6, 1.2]	1024	0.9 [0.7, 1.1]	0.9 [0.6, 1.3]	0.9 [0.6, 1.2]	0.8 [0.6, 1.1]	0.9 [0.7, 1.2]	0.566
Total cholesterol (g/L)	2.1 (0.4)	1024	2.1 (0.4)	2.1 (0.4)	2.1 (0.4)	2.0 (0.4)	2.1 (0.4)	0.016
HDL cholesterol (g/L)	0.6 [0.5, 0.7]	1024	0.6 [0.5, 0.7]	0.6 [0.5, 0.7]	0.6 [0.5, 0.7]	0.5 [0.5, 0.6]	0.6 [0.5, 0.6]	0.389
LDL cholesterol (g/L)	1.3 (0.3)	1023	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.4 (0.4)	0.037
Dyslipidemia (%)	136 (13.2)	1028	21.0	12.7	12.1	11.4	18.2	0.146
Lipid-lowering TTx (%)	93 (9.0)	1028	19.8	8.8	7.5	8.5	9.1	0.013
Serum creatinine (mg/L)	7.9 [7.0, 9.0]	1024	7.7 [6.7, 8.8]	7.5 [6.8, 8.7]	7.9 [7.0, 8.9]	8.2 [7.2, 9.3]	8.1 [7.2, 9.5]	<0.001
eGFR (ml/min/1.73m <sup>2</sup> )	100.9 [90.2, 112.9]	1024	97.9 [87.5, 103.1]	99.7 [90.2, 113.1]	102.0 [90.9, 113.9]	102.6 [90.6, 113.0]	97.9 [87.7, 113.5]	0.017
Change in eGFR between V4 and V1	-6.2 [-17.9, 3.8]	911	-5.0 [-11.1, 3.6]	-3.1 [-14.4, 6.2]	-7.3 [-19.7, 3.4]	-7.0 [-21.6, 0.8]	-5.3 [-12.4, 7.0]	0.004
ACR ≥ 1.336 (mg/mmol) (%)	103 (10.1)	1021	13.8	11.8	9.4	7.6	13.0	0.333

	<b>Overall</b>	<b>N</b>	<b>≤ 2.5 kg</b>	<b>2.5 - 3 kg</b>	<b>3 - 3.5 kg</b>	<b>3.5 - 4 kg</b>	<b>&gt; 4 kg</b>	<b>p</b>
NGAL (NPX)	2.3 [2.2, 2.5]	949	2.3 [2.2, 2.5]	2.3 [2.2, 2.4]	2.3 [2.2, 2.5]	2.3 [2.2, 2.5]	2.3 [2.2, 2.5]	1.000
SBP 24h (mmHg)	118 [112, 125]	945	121 [115, 127]	117 [112, 124]	118 [112, 124]	118 [112, 125]	118 [112, 124]	0.077
DBP 24h (mmHg)	73 [69, 78]	945	74 [70, 79]	73 [69, 78]	73 [69, 78]	73 [69, 78]	72 [69, 75]	0.284
Treated hypertension (%)	131 (12.9)	1019	19.0	17.2	12.0	7.3	16.9	0.004
Hypertension (%)	282 (33.6)	840	47.9	38.9	31.9	25.8	33.9	0.009
Index LVM (g/height <sup>2.7</sup> )	31.4 [26.3, 37.6]	1016	32.0 [27.2, 38.4]	30.6 [24.8, 36.2]	31.1 [26.0, 37.4]	31.7 [26.8, 38.8]	33.6 [28.8, 41.0]	0.040
cIMT (μm)	563.5 [494.8, 669.8]	1006	614.2 [545.9, 687.5]	579.9 [492.0, 687.5]	557.6 [492.3, 644.4]	533.0 [485.6, 668.6]	616.0 [505.0, 743.0]	<0.001
PWV (m/s)	7.8 [7.0, 8.8]	1008	8.0 [7.2, 9.1]	7.8 [7.0, 8.5]	7.7 [7.0, 8.6]	7.9 [7.1, 8.8]	8.0 [7.2, 9.1]	0.051
Distensibility (kPa <sup>-1</sup> 10 <sup>-3</sup> )	43.6 [29.1, 60.8]	971	33.8 [25.9, 52.0]	39.6 [27.6, 54.9]	47.9 [30.8, 64.8]	47.1 [31.9, 63.2]	40.2 [27.1, 59.3]	<0.001
Diastolic dysfunction (%)	124 (12.3)	1009	16.5	12.9	11.4	9.1	21.3	0.052

BMI, body mass index; WC, waist circumference; TTX, treatment; HDL, high density lipoproteins; LDL, low density lipoproteins; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; NGAL: neutrophil gelatinase-associated lipocalin; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVM, left ventricular mass; cIMT, carotid intima-media thickness; PWV, pulse wave velocity.

P-values for education, income, BMI class, waist circumference class, prematurity, breastfeeding, anti-diabetic treatment, diabetes, hypertension and diastolic dysfunction were calculated using Fisher's exact test (Monte Carlo simulation with 2000 replicates).

Generation 2 refers to the children (and their spouse) of those who came to the first visit as adults. At the 4th visit, most participants were adults.

High waist circumference was defined as greater than 102 and 88 cm for men and women, respectively.

NGAL was measured using the Olink technology (see <https://www.olink.com>) which provides log<sub>2</sub> normalized protein expression with relative quantification.

Hypertension was defined as treated, declared, or based on 24h-ABPM (>130 mmHg SBP or > 80 mmHg DBP).

Physical activity was assessed using the International Physical Activity Questionnaire.



**Table 2: Association of birth weight with dichotomous cardiovascular and renal outcomes at visit 4**

Outcome	N event/N	OR (95% CI) Model 1	P-value Model 1	OR (95% CI) Model 2	P-value Model 2	OR (95% CI) Model 3	P-value Model 3	OR (95% CI) Model 4	P-value Model 4
Cardiovascular outcomes									
DD	101/816	0.69 [0.33 - 1.41]	0.302			1.09 [0.74 - 1.6]	0.656	1.09 [0.75 - 1.59]	0.65
Treated hypertension	96/822	0.74 [0.47 - 1.14]	0.16			0.67 [0.45 - 0.99]	0.039	0.72 [0.48 - 1.06]	0.091
Hypertension	223/683	0.71 [0.54 - 0.94]	0.013	0.61 [0.45 - 0.84]	0.002	0.55 [0.39 - 0.77]	<0.001	0.58 [0.42 - 0.81]	<0.001
Renal outcomes									
ACR	82/827	0.81 [0.53 - 1.24]	0.337			0.86 [0.55 - 1.32]	0.485	0.87 [0.56 - 1.34]	0.519

DD: diastolic dysfunction; ACR: albumin-to-creatinine ratio.

Model 1 was crude,

Model 2 was adjusted for age, sex, generation, smoking status, education level and physical activity for hypertension and also for HDL, LDL, triglycerides, SBP, glucose, anti-hypertensive TTx, anti-diabetic TTx and lipid-lowering TTx.

(only age, sex, generation and smoking status for diastolic dysfunction, treated hypertension and albuminuria).

Model 3 was the model 2 + BMI class and model 4 was the model 2 + waist circumference class.

**Table 3: Association of birth weight with continuous cardiovascular and renal outcomes at visit 4**

Outcome	N	Beta (95% CI) Model 1	P-value Model 1	Beta (95% CI) Model 2	P-value Model 2	Beta (95% CI) Model 3	P-value Model 3	Beta (95% CI) Model 4	P-value Model 4
Cardiovascular outcomes									
LVM	819	*	0.001	*	0.015	*	0.299	*	0.073
PWV	818	1.01 [0.99;1.03]	0.343	1.01 [0.99;1.03]	0.258	1.01 [0.99;1.03]	0.205	1.01 [0.99;1.03]	0.263
cIMT	812	1 [0.97;1.02]	0.891	1 [0.98;1.02]	0.78	Normal: 1.01 [0.98;1.04] Overweight: 0.95 [0.92;0.99] Obese: 1.02 [0.98;1.06]	0.026	1 [0.98;1.02]	0.662
Distensibility	784	2.89 [- 0.2;5.98]	0.066	1.86 [-0.54;4.25]	0.13	Normal: 5.09 [1.8;8.38] Overweight: 0.95 [0.87;1.03] Obese: 1.01 [0.92;1.1]	0.011	2.19 [- 0.22;4.59]	0.078
Renal outcomes									
eGFR	830	0.35 [- 1.41;2.11]	0.695	0.19 [-1.11;1.5]	0.774	0.24 [-1.08;1.55]	0.727	0.2 [- 1.11;1.51]	0.768
eGFR decline	738	-0.59 [- 2.83;1.65]	0.60	0.4 [-1.66;2.46]	0.71	0.45 [-1.63;2.51]	0.68	0.47 [- 1.6;2.52]	0.66
NGAL	768	0 [-0.03;0.03]	0.851	-0.01 [-0.04;0.02]	0.48	-0.01 [-0.04;0.02]	0.55	-0.01 [- 0.04;0.02]	0.502

<b>Outcome</b>	<b>N</b>	<b>Beta (95% CI) Model 1</b>	<b>P-value Model 1</b>	<b>Beta (95% CI) Model 2</b>	<b>P-value Model 2</b>	<b>Beta (95% CI) Model 3</b>	<b>P-value Model 3</b>	<b>Beta (95% CI) Model 4</b>	<b>P-value Model 4</b>
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LVM, left ventricular mass; PWV, pulse wave velocity; cIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; NGAL: neutrophil gelatinase-associated lipocalin.

PWV, cIMT and distensibility were log-transformed to improve model fit. Results are presented on the exponential scale ( $\exp(\text{beta})$ ). Model 1 was crude, model 2 was adjusted for age, sex, generation, smoking status, education level and physical activity at the 4<sup>th</sup> visit. and also for HDL, LDL, triglycerides, SBP, glucose, anti-hypertensive TTx, anti-diabetic TTx and lipid-lowering TTx. Model 3 = Model 2 +BMI class and Model 4 = Model 2 + waist circumference class.

\*: the effects of birth weight on LVM (left ventricular mass) were non-linear.

**Table S1: Sensitivity analyses for the association between birth weight and each outcome without prematurity and CV diseases**

Outcome	N or event/N	Beta (95% CI) Model 1	P-value Model 1	Beta (95% CI) Model 2	P-value Model 2	Beta (95% CI) Model 3	P-value Model 3	Beta (95% CI) Model 4	P-value Model 4
CV outcomes									
LVM	769	*	< 0.001	*	0.016	*	0.267	*	0.069
PWV	767	1.01 [0.99;1.03]	0.457	1.01 [1;1.03]	0.138	1.01 [1;1.03]	0.122	1.01 [1;1.03]	0.144
cIMT	763	1 [0.97;1.02]	0.742	1 [0.98;1.02]	0.862	Normal: 1.02 [0.99;1.05] Overweight: 0.95 [0.92;0.99] Obese: 1.02 [0.98;1.07]	0.009	1 [0.98;1.02]	0.97
Distensibility	736	3.88 [0.65;7.11]	0.018	1.99 [-0.54;4.53]	0.13	Normal: 6.12 [2.48;9.74] Overweight: 0.94 [0.87;1.03] Obese: 1 [0.91;1.1]	0.003	2.41 [-0.13;4.95]	0.066
Renal outcomes									
eGFR	778	0.78 [-1.04;2.6]	0.4	0.1 [-1.25;1.46]	0.882	0.19 [-1.17;1.56]	0.784	0.14 [-1.23;1.5]	0.846
eGFR decline	694	-0.86 [-3.24;1.52]	0.48	0.97 [-1.22;3.15]	0.39	1.03 [-1.17;3.22]	0.37	1.03 [-1.15;3.22]	0.36
NGAL	722	-0.01 [-0.04;0.02]	0.635	-0.02 [-0.05;0.02]	0.347	-0.01 [-0.04;0.02]	0.41	-0.01 [-0.05;0.02]	0.377

<b>Outcome</b>	<b>N or N event/N</b>	<b>Beta (95% CI) Model 1</b>	<b>P-value Model 1</b>	<b>Beta (95% CI) Model 2</b>	<b>P-value Model 2</b>	<b>Beta (95% CI) Model 3</b>	<b>P-value Model 3</b>	<b>Beta (95% CI) Model 4</b>	<b>P-value Model 4</b>
<b>Outcome</b>	<b>N or N event/N</b>	<b>OR (95% CI) Model 1</b>	<b>P-value Model 1</b>	<b>OR (95% CI) Model 3</b>	<b>P-value Model 3</b>	<b>OR (95% CI) Model 4</b>	<b>P-value Model 4</b>	<b>OR (95% CI) Model 5</b>	<b>P-value Model 5</b>
DD	94/767	0.66 [0.31 - 1.41]	0.283			1.1 [0.75 - 1.61]	0.612	1.1 [0.76 - 1.61]	0.607
Treated hypertension	92/775	0.3 [0.13 - 0.68]	<0.001			0.65 [0.43 - 0.98]	0.035	0.69 [0.45 - 1.05]	0.077
Hypertension	208/644	0.68 [0.51 - 0.91]	0.009	0.62 [0.44 - 0.87]	0.004	0.54 [0.38 - 0.78]	<0.001	0.58 [0.41 - 0.82]	0.002
ACR	75/776	0.67 [0.3 - 1.47]	0.316			0.88 [0.39 - 1.96]	0.745	0.93 [0.41 - 2.07]	0.852

CV, cardiovascular; LVM, left ventricular mass; PWV, pulse wave velocity; cIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; NGAL: neutrophil gelatinase-associated lipocalin; DD: diastolic dysfunction; ACR: albumin-to-creatinine ratio.

PWV, cIMT and DD were log-transformed to improve model fit. Results are presented using the exponential scale ( $\exp(\beta)$ ).

Model 1 was crude, model 2 was adjusted for age, sex, generation, smoking status, education level and physical activity (only age, sex, generation and smoking status for diastolic dysfunction, treated hypertension and albuminuria). and also for HDL, LDL, triglycerides, SBP, glucose, anti-hypertensive TTx, anti-diabetic TTx and lipid-lowering TTx.

Model 3 was the model 2 + BMI class and model 4 was the model 2 + waist circumference class.

\*: the effects of birth weight on LVM were non-linear.

**Table S2: Percentage of variance decomposition for birth weight**

	Heritability (%)	Covariates effect (%)	Residual effect (%)
With Kinship (n=2092)	44.03	3.54	52.43
With GRM (n=956)	42.52	2.05	55.43
With Kinship (n=956)	42.06	2.01	55.93

GRM: genetic relatedness matrix

For the first model, all subjects with reported birth weight (BW) were included (n=2092) while for the second model, only subjects with successful genetic data were included (n=956).